wherein the compound of Formula IV and the compound of Formula I or III are present in a 4:1 ratio by weight, and the combined concentration of the compound of Formula IV and the compound of Formula I or III is from about 70 mg/mL to about 150 mg/mL, at an infusion rate of from about 100 mL/hr to about 400 mL/hr.

REMARKS

The present application is a division of patent application Serial No. 09/121,567 filed July 23, 1998, and now allowed. The present application has been amended to recite the relationship to its parent case. The claims have been amended to put them in condition for allowance. The amendments to claims 7-9, 15 and 16 find support in original claim11; the amendments to claims 17-20 find support in original claim 21; the amendments to claim 28 find support in original claim 31; and the amendment to claim 34 finds support in original claim37. A marked-up version of the claim amendments is attached hereto. Claims 1-6, 21-27, 31-33 and 37-39 are cancelled. Claims 7-10, 15, 16, 17-20, 28-30 34-36 and 40-45 are now pending.

In view of the above Amendments, Applicant believes that all of the pending claims are allowable. The Examiner is invited to contact the undersigned at (713) 787-1438 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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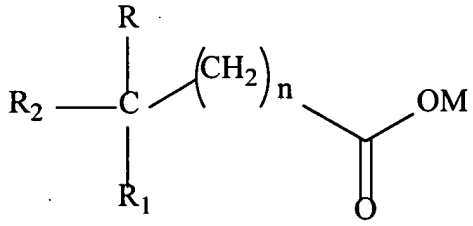
(713) 787-1400

Date: May 22, 2001

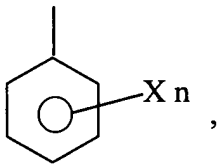
MARKED-UP VERSION OF THE PENDING CLAIMS

7. (Amended) A pharmaceutical composition, comprising <u>in solution</u>:

a compound of Formula IV:



wherein R and R_1 are independently selected from the group consisting of H, lower alkoxy (C_{1-6}), and lower alkyl (C_{1-6}); R_2 is selected from Formula II: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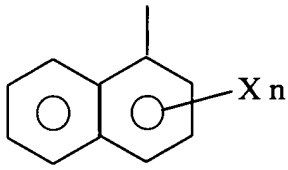
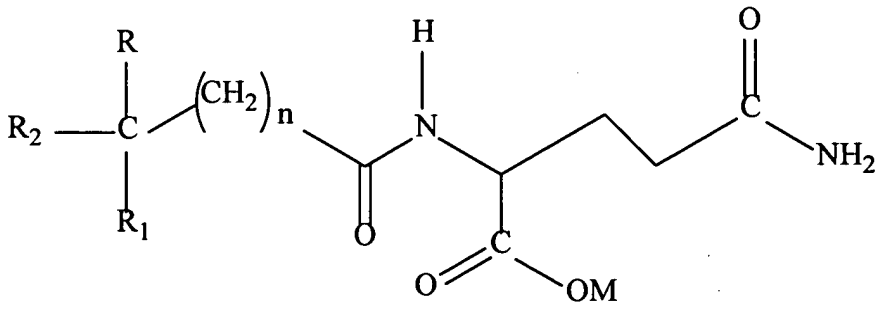
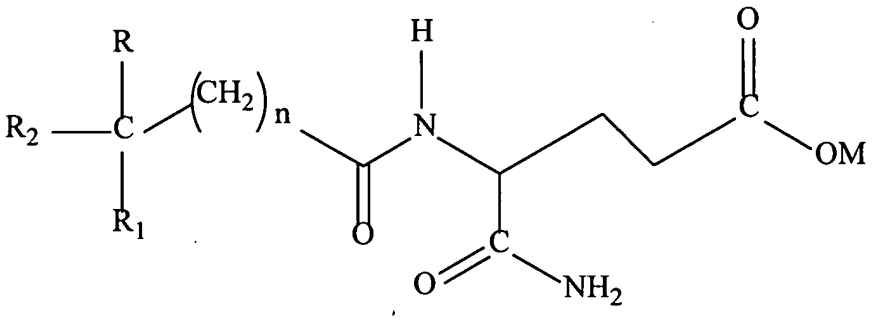

,

wherein X is a halogen, lower alkyl (C_{1-6}), lower alkoxy (C_{1-6}), cycloalkyl, cycloalkoxy, aryl (C_{6-12}), substituted aryl or hydroxy and n is 0, 1, 2, 3, or 4; M is hydrogen, a salt forming cation, alkyl (C_{1-6}), cycloalkyl, or aryl (C_{6-12}); and n is 0-5; and

a compound of Formula I:



or Formula III



wherein n is 0, 1, 2, 3, 4, or 5; M is hydrogen, a salt forming cation, an alkyl (C_{1-6}), a cycloalkyl, or an aryl (C_{6-12});R and R_1 are independently selected from the group consisting of H, lower alkoxy (C_{1-6}), and lower alkyl (C_{1-6}); R_2 is selected from Formula II;

wherein the compound of Formula IV and the compound of Formula I are present in about a 4:1 ratio by weight; and

water sufficient to form an aqueous solution of the compound of Formula IV and the compound of Formula I wherein the combined concentration of the compound of Formula IV and the compound of Formula I is from about 70 mg/mL to about 150 mg/mL.

8. (Amended) The pharmaceutical composition of claim 7, wherein in the compound of Formula IV, M is hydrogen or sodium; n is 0; R is H or C_3H_7; R_1 is selected from the group consisting of H, CH_3, CH_3-O-, C_2H_5, and C_3H_7; R_2 is selected from Formula II, wherein X is Cl, F, or OH; and wherein in the compound of Formula I or III, M is hydrogen or sodium; n is 0; R is H or C_3H_7; R_1 is selected from the group consisting of H, CH_3, CH_3-O-, C_2H_5, and C_3H_7; R_2 is selected from Formula II, wherein X is Cl, F, or OH.

9. (Amended) The pharmaceutical composition of claim 7, wherein the compound of Formula IV is phenylacetic acid or pharmaceutically acceptable salts thereof, and the compound of

Formula I is phenylacetylglutamine or pharmaceutically acceptable salts thereof, or the compound of Formula III is phenylacetylisoglutamine or pharmaceutically acceptable salts thereof.

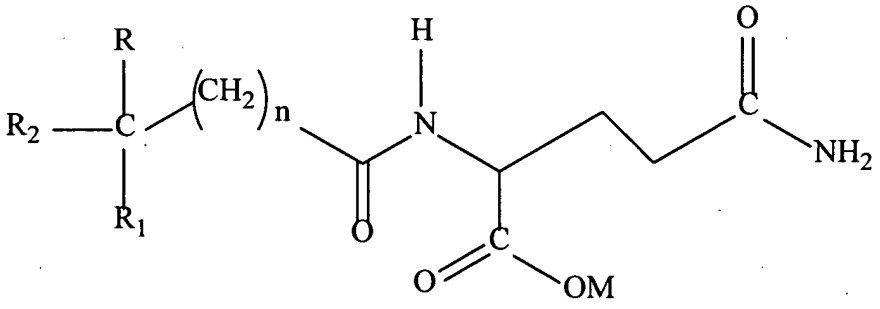
10. The pharmaceutical composition of claim 9, wherein the combined concentration is about 80 mg/mL.

15. (Amended) The pharmaceutical composition of claim ~~11~~ 7, wherein the compound of Formula IV and the compound of Formula I or III are present in a 4:1 ratio by weight.

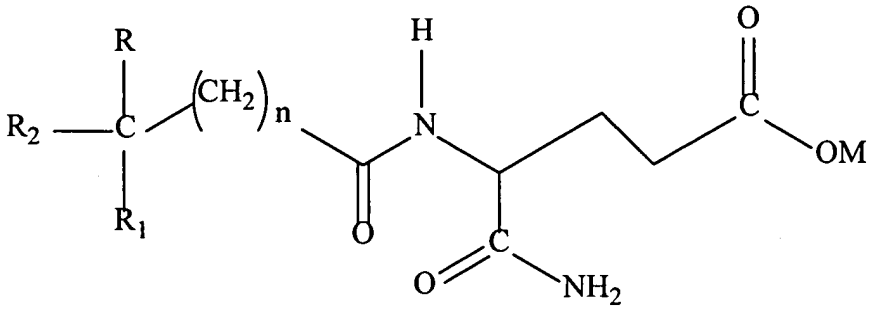
16. (Amended) The pharmaceutical composition of claim ~~11~~ 7further comprising water sufficient to form an aqueous solution of the compound of Formula IV and the compound of Formula I or III wherein the combined concentration of the compound of Formula IV and the compound of Formula I or III is from about 70 mg/mL to about 150 mg/mL.

17. (Amended) A pharmaceutical composition, comprising in solution:

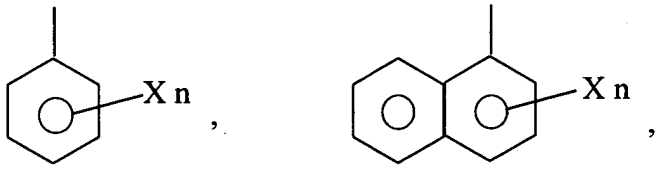
a compound of Formula I:



or Formula III



wherein R and R_1 are independently selected from the group consisting of H, lower alkoxy (C_{1-6}), and lower alkyl (C_{1-6}); R_2 is selected from Formula II:



wherein X is a halogen, lower alkyl (C_{1-6}), lower alkoxy (C_{1-6}), cycloalkyl, cycloalkoxy, aryl (C_{6-12}), substituted aryl or hydroxy and n is 0, 1, 2, 3, or 4; M is hydrogen, a salt forming cation, alkyl (C_{1-6}), cycloalkyl, or aryl (C_{6-12}); and n is 0-5; said compound of Formula I being a racemic mixture, L or R optic isomer, or mixtures thereof; and

a pharmaceutically acceptable diluent.

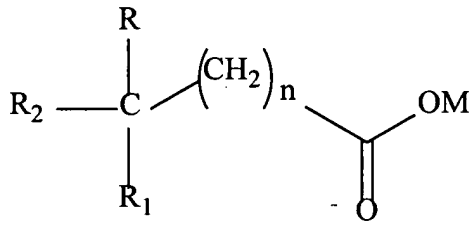
18. (Amended) The pharmaceutical composition of claim 17, wherein in the compound of Formula I <u>or III,</u> M is hydrogen or sodium; n is 0; R is H or C_3H_7; R_1 is selected from the group consisting of H, CH_3, CH_3-O-, C_2H_5, and C_3H_7; R_2 is selected from Formula II, wherein X is Cl, F, or OH.

19. (Amended) The pharmaceutical composition of claim 17, wherein the compound of Formula I is phenylacetylglutamine <u>or the compound of Formula III is phenylacetyisoglutamine,</u> or pharmaceutically acceptable salts thereof.

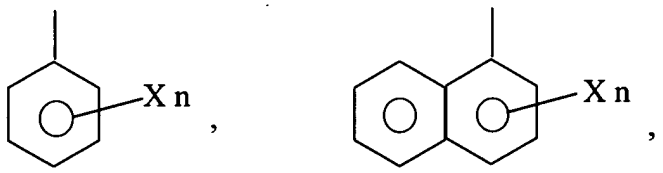
20. (Amended) The pharmaceutical composition of claim 17, further comprising water sufficient to form an aqueous solution ~~of the phenylacetylglutamine~~ in a concentration ranging from about 200 mg/mL to about 350 mg/mL.

28. (Amended) A method of treating neoplastic disease, comprising:

administering to a patient at an infusion rate of from about 100 mL/hr to about 400 mL/hr of a pharmaceutical composition, the pharmaceutical composition comprising an aqueous solution of a compound of Formula IV:

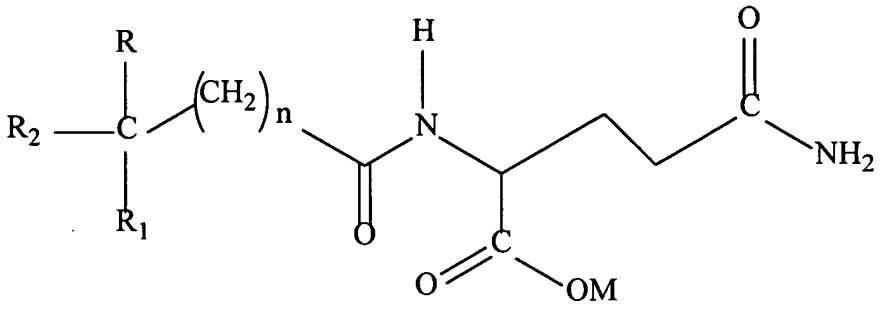


wherein R and R_1 are independently selected from the group consisting of H, lower alkoxy (C_{1-6}), and lower alkyl (C_{1-6}); R_2 is selected from Formula II:

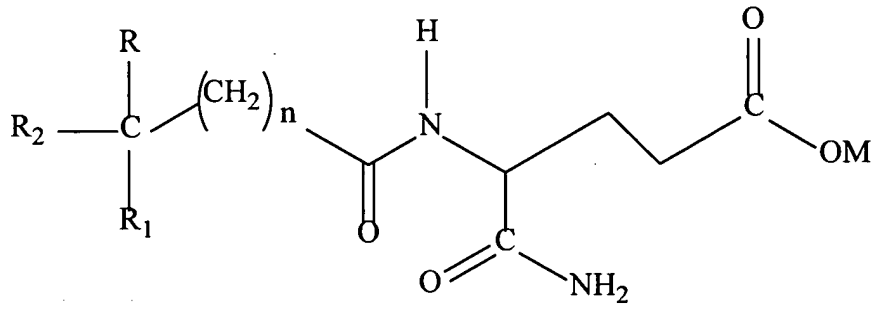


wherein X is a halogen, lower alkyl (C_{1-6}), lower alkoxy (C_{1-6}), cycloalkyl, cycloalkoxy, aryl, substituted aryl (C_{6-12}) or hydroxy and n is 0, 1, 2, 3, or 4; M is hydrogen, a salt forming cation, alkyl (C_{1-6}), cycloalkyl, or aryl (C_{6-12}); and n is 0-5; and,

a compound of Formula I:



or Formula III



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wherein n is 0, 1, 2, 3, 4, or 5; M is hydrogen, a salt forming cation, an alkyl (C_{1-6}), a cycloalkyl, or an aryl (C_{6-12}); R and R_1 are independently selected from the group consisting of H, lower alkoxy (C_{1-6}), and lower alkyl (C_{1-6}); R_2 is selected from Formula II;

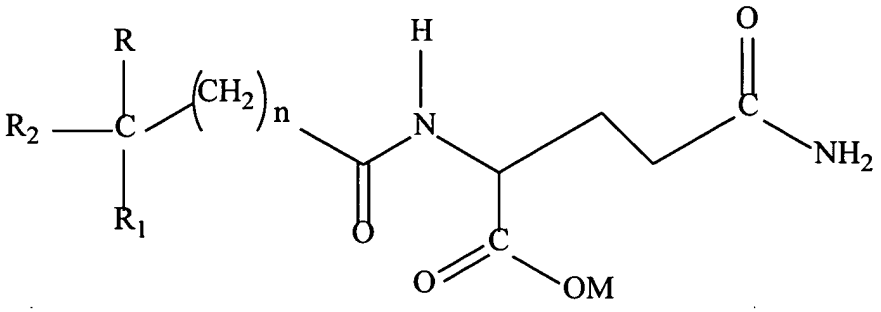
wherein the compound of Formula IV and the compound of Formula I or III are present in a 4:1 ratio by weight, and the combined concentration of the compound of Formula IV and the compound of Formula I or III is from about 70 mg/mL to about 150 mg/mL.

29. The method of claim 28, wherein the infusion rate is about 250 mL/hr to about 300 mL/hr, and further comprising performing the administering step sufficiently often to reach a dosage level of from about 0.1 g/kg/day to about 2.6 g/kg/day.

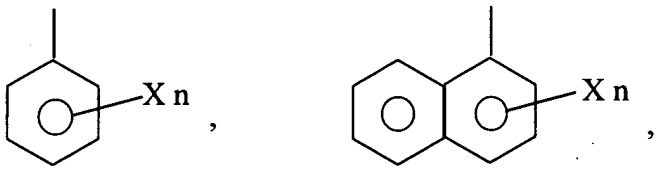
30. The method of claim 29, wherein the dosage level is from about 0.2 g/kg/day to about 0.9 g/kg/day.

34. (Amended) A method of treating neoplastic disease, comprising:

administering to a patient a first pharmaceutical composition, the first pharmaceutical composition comprising an aqueous solution of a compound of Formula I:

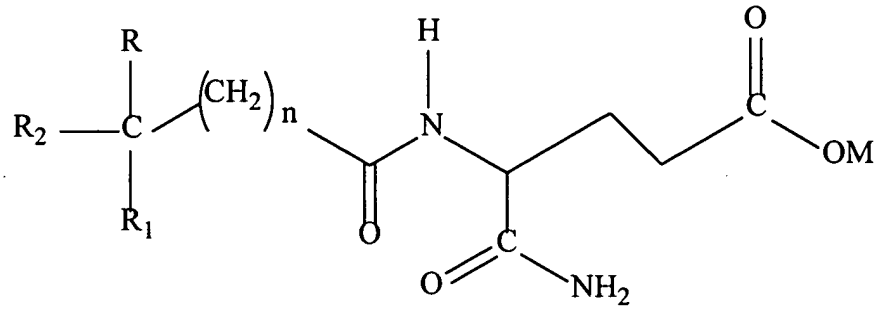


wherein R and R_1 are independently selected from the group consisting of H, lower alkoxy (C_{1-6}), and lower alkyl (C_{1-6}); R_2 is selected from Formula II:



wherein X is a halogen, lower alkyl (C_{1-6}), lower alkoxy (C_{1-6}), cycloalkyl, cycloalkoxy, aryl (C_{6-12}), substituted aryl or hydroxy and n is 0, 1, 2, 3, or 4; M is hydrogen, a salt forming cation, alkyl (C_{1-6}), cycloalkyl, or aryl (C_{6-12}); and n is 0-5; and

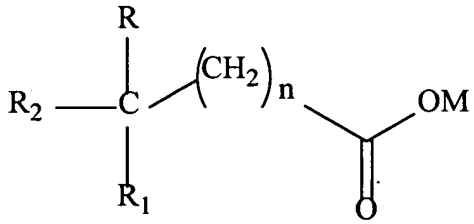
a compound of Formula III:



wherein n is 0, 1, 2, 3, 4, or 5; M is hydrogen, a salt forming cation, an alkyl (C_{1-6}), a cycloalkyl, or an aryl (C_{6-12}); R and R_1 are independently selected from the group consisting of H, lower alkoxy (C_{1-6}), and lower alkyl (C_{1-6}); R_2 is selected from Formula II;

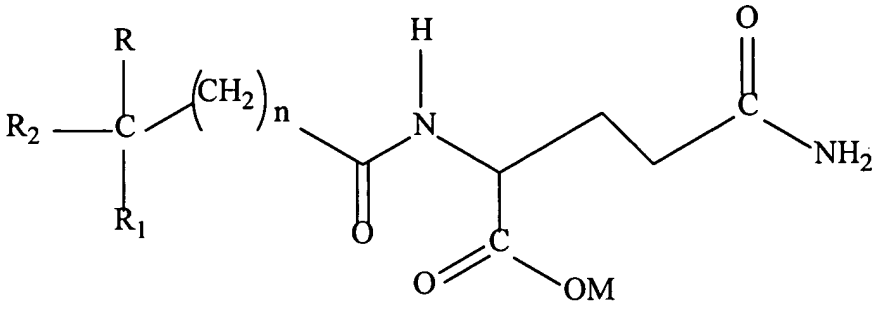
wherein the compound of Formula I is present in a 4:1 ratio by weight to the compound of Formula III and the combined concentration of the compound of Formula I and the compound of Formula III is from about 200 mg/mL to about 350 mg/mL, at an infusion rate of from about 100 mL/hr to about 400 mL/hr;

and a second pharmaceutical composition, the second pharmaceutical composition comprising an aqueous solution of a compound of Formula IV:

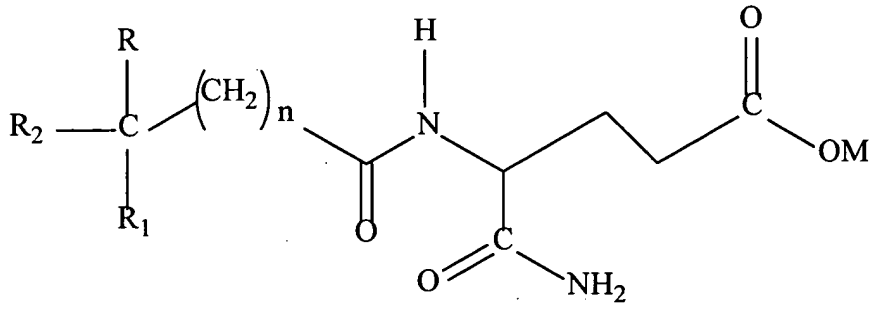


wherein R and R_1 are independently selected from the group consisting of H, lower alkoxy (C_{1-6}), and lower alkyl (C_{1-6}); R_2 is selected from Formula II; and

a compound of Formula I:



or Formula III



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wherein n is 0, 1, 2, 3, 4, or 5; M is hydrogen, a salt forming cation, an alkyl (C_{1-6}), a cycloalkyl, or an aryl (C_{6-12}); R and R_1 are independently selected from the group consisting of H, lower alkoxy (C_{1-6}), and lower alkyl (C_{1-6}); R_2 is selected from Formula II;

wherein the compound of Formula IV and the compound of Formula I or III are present in a 4:1 ratio by weight, and the combined concentration of the compound of Formula IV and the compound of Formula I or III is from about 70 mg/mL to about 150 mg/mL, at an infusion rate of from about 100 mL/hr to about 400 mL/hr.

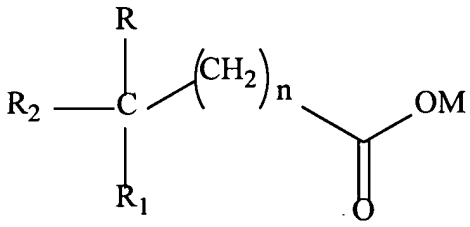
35. The method of claim 34, wherein the infusion rate of the first pharmaceutical composition is about 250 mL/hr to about 300 mL/hr and the infusion rate of the second pharmaceutical composition is about 250 mL/hr to about 300 mL/hr, and further comprising

performing the administering step sufficiently often to reach a dosage level of the first pharmaceutical composition of from about 0.6 g/kg/day to about 25 g/kg/day and a dosage level of the second pharmaceutical composition of from about 0.1 g/kg/day to about 2.6 g/kg/day.

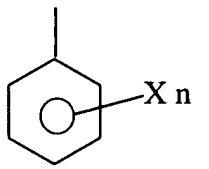
36. The method of claim 35, wherein the dosage level of the first pharmaceutical composition is from about 5.0 g/kg/day to about 12.0 g/kg/day, and wherein the dosage level of the second pharmaceutical composition is from about 0.2 g/kg/day to about 0.9 g/kg/day.

40. A method of treating neoplastic disease, comprising:

administering to a patient at an infusion rate of from about 100 mL/hr to about 400 mL/hr of a pharmaceutical composition, the pharmaceutical composition comprising an aqueous solution of a compound of Formula IV:



wherein R and R_1 are independently selected from the group consisting of H, lower alkoxy (C_{1-6}), and lower alkyl (C_{1-6}); R_2 is selected from Formula II: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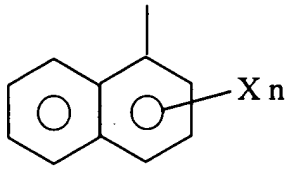
,

wherein X is a halogen, lower alkyl (C_{1-6}), lower alkoxy (C_{1-6}), cycloalkyl, cycloalkoxy, aryl, substituted aryl (C_{6-12}) or hydroxy and n is 0, 1, 2, 3, or 4; M is hydrogen, a salt forming cation, alkyl (C_{1-6}), cycloalkyl, or aryl (C_{6-12}); and n is 0-5; and,

wherein the concentration of the compound of Formula IV is from about 70 mg/mL to about 150 mg/mL.

41. The method of claim 40, wherein the infusion rate is about 250 mL/hr to about 300 mL/hr, and further comprising performing the administering step sufficiently often to reach a dosage level of from about 0.1 g/kg/day to about 2.6 g/kg/day.

42. The method of claim 41, wherein the dosage level is from about 0.2 g/kg/day to about 0.9 g/kg/day.

43. The method of claim 40, wherein the compound of Formula IV is phenylacetic acid or pharmaceutically acceptable salts thereof.

44. The method of claim 40, wherein the compound of Formula IV is a precursor compound.

45. The method of claim 44, wherein the precursor compound of Formula IV is phenylbutyric acid or its pharmaceutically acceptable salts thereof.